An overview of angioedema: Pathogenesis and causes

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INTRODUCTION — Angioedema is self-limited, localized swelling of the skin or mucosal tissues, which results from extravasation of fluid into the interstitium due to a loss of vascular integrity. Angioedema may occur in isolation, accompanied by urticaria, or as a component of anaphylaxis.

The pathogenesis and causes of angioedema will be reviewed here. The clinical features, diagnosis, differential diagnosis, and management of acute angioedema are discussed separately. (See "An overview of angioedema: Clinical features, diagnosis, and management".)

EPIDEMIOLOGY — Data regarding the epidemiology of angioedema is limited. In a retrospective review of all hospital admissions in New York State over 13 years, angioedema was the second most common "allergic" disease to necessitate hospitalization, exceeded only by asthma [1]. The number of hospitalizations per year more than doubled during the study period, suggesting that the prevalence may be increasing. African Americans were disproportionately affected, as they accounted for 42 percent of the admissions for angioedema, but only 16 percent of the state's population.

The epidemiology of specific forms of angioedema, such as hereditary angioedema due to C1 inhibitor deficiency, is discussed elsewhere. (See "Clinical manifestations and pathogenesis of hereditary angioedema".)

PATHOGENESIS — Angioedema results from a loss of vascular integrity that allows fluid to move into tissues. Exposure of the vasculature to inflammatory mediators causes dilation and increased permeability of capillaries and venules.

In contrast, edema associated with cardiovascular, renal, and liver disease (eg, heart failure, renal failure, venous obstruction) is usually due to an alteration in Starling's forces, such as an increase in intracapillary pressure or a reduction in the plasma oncotic pressure (ie, any cause of severe hypoalbuminemia) in the presence

of normal vasculature. (See "Pathophysiology and etiology of edema in adults".)

CAUSES — The known causes of angioedema can be subdivided into three groups, depending upon the underlying mechanism:

- Mast cell-mediated etiologies, in which angioedema results from release of mast cell-derived mediators that increase vascular permeability. Mast cell mediated angioedema is associated with urticaria and/or pruritus in most cases.

- Bradykinin-mediated etiologies, in which angioedema results from the generation of bradykinin and complement-derived mediators that increase vascular permeability. These forms of angioedema are not associated with urticaria and/or pruritus and are diagnosed and treated differently from other types of angioedema. (See "An overview of angioedema: Clinical features, diagnosis, and management".)

- Etiologies of unknown mechanism.

Mast cell-mediated etiologies — Mast cell-mediated angioedema is associated with urticaria and/or pruritus in most cases. This form of angioedema is pathologically similar to urticaria, although it takes place in the deeper levels of the dermis and subcutaneous tissues. Mast cells can be activated via several mechanisms (table 1). (See "Mast cells: Development, identification, and physiologic roles" and "Mast cells: Surface receptors and signal transduction".)

Activated mast cells release inflammatory mediators, including histamine, heparin, leukotriene C4, and prostaglandin D2, which cause dilation of venules in the dermis and enhance venule permeability, with resultant tissue edema. (See "Mast cell derived mediators".)

The treatment of mast cell-mediated angioedema is discussed separately. (See "An overview of angioedema: Clinical features, diagnosis, and management".)

Allergic reactions — Acute angioedema, with or without other symptoms of allergic reactions, may be triggered by foods, drugs, latex, exercise, the stings of various insects, and a growing list of other uncommon allergens. This type of angioedema is most often seen in patients with other allergic conditions, such as allergic rhinitis, food allergies, asthma, and atopic dermatitis.

Angioedema resulting from an allergic reaction is usually accompanied by other signs and symptoms, including urticaria, pruritus, flushing, throat tightness, bronchospasm, and hypotension. Angioedema can occur in isolation, although this is uncommon. As an example, in a series of 112 patients with penicillin allergy confirmed by skin testing, only one patient had experienced isolated angioedema without urticaria during the presenting allergic reaction [2].

The classic type of allergic reaction results from IgE-mediated, Gell and Coombs

type I hypersensitivity (table 2). The reaction typically occurs within minutes to two hours following exposure to the trigger. However, IgE-mediated allergic reactions are occasionally delayed in onset. Allergy to certain meats (lamb, beef, and/or pork) can lead to reactions with prominent angioedema, beginning two to six hours after ingestion [3].

Direct mast cell release — Mast cells can be nonspecifically stimulated to release their proinflammatory mediators by certain medications and pharmaceuticals, such as opiates and radiocontrast media. This type of angioedema is accompanied by urticaria in most cases. IgE is not involved, and skin testing or in vitro testing is not helpful. (See "Immediate hypersensitivity reactions to radiocontrast media".)

Aspirin and NSAIDs — Nonsteroidal antiinflammatory drugs (NSAIDs), such as aspirin and ibuprofen, can cause acute urticaria/angioedema and can exacerbate chronic urticaria/angioedema. (See 'Chronic urticaria with or without angioedema' below.)

This adverse effect of NSAIDs is believed to be due to the pharmacologic properties of the medications on mast cells. NSAIDs inhibit the enzyme cyclooxygenase 1 (COX 1), the enzyme which mediates the generation of prostaglandins from arachidonic acid within mast cells and other leukocytes. NSAID administration results in increased formation of proinflammatory cysteinyl leukotrienes, leading to angioedema in some individuals.

NSAIDs that nonselectively inhibit both COX 1 and 2 enzymes (aspirin, ibuprofen, and most others) can potentially induce this effect. Selective COX 2 inhibitors, such as celecoxib, are tolerated by most patients who have reacted to nonselective NSAIDs [4], although rare exceptions are reported [5]. Management of patients with these reactions is reviewed separately. (See "NSAIDs (including aspirin): Allergic and pseudoallergic reactions", section on 'Management'.)

Chronic urticaria with or without angioedema — Chronic urticaria refers to recurrent urticaria that is present most days of the week for a period of six weeks or longer. Angioedema is present in up to 50 percent of patients with chronic urticaria, and most affected patients have hives regularly and angioedema occasionally when the symptoms are most severe.

Chronic urticaria may persist over months to years and is most common in women, particularly between the ages of 40 and 50 years. In most cases of chronic urticaria/angioedema, a specific cause cannot be identified. This disorder is reviewed in more detail separately. (See "Chronic urticaria: Diagnosis, theories of pathogenesis, and natural history" and "Chronic urticaria: Standard management and patient education".)

Bradykinin-mediated etiologies — Angioedema can occur due to vasodilation and increased vascular permeability resulting from inflammatory mediators, especially bradykinin, generated by other cell types. Mast cells are not believed to be involved in this form of angioedema, and pruritus and urticaria are absent.

Perturbations in kinin pathways resulting directly from the actions of medications (eg, angiotensin converting enzyme inhibitors) or from defects in the complement system are the main causes of bradykinin-mediated angioedema. The treatment of bradykinin-induced angioedema is discussed separately. (See "An overview of angioedema: Clinical features, diagnosis, and management".)

ACE inhibitors — Angioedema occurs in 0.1 to 0.7 percent of patients treated with angiotensin converting enzyme (ACE) inhibitors [6-9]. It is not related to ACE inhibitor-induced cough, which is much more common. (See "Major side effects of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers".)

ACE inhibitors accounted for 20 to 30 percent of all angioedema cases presenting to emergency departments in both community and tertiary-care settings [10-12]. Patients with ACE inhibitor-induced angioedema are typically older and lack a history of other allergic disorders. Black patients may be more susceptible [7,13-16], although this has not been a consistent finding in all studies [12].

- ACE inhibitor-induced angioedema typically involves the lips, tongue, mouth, larynx, pharynx, and subglottic tissues [17]. Urticaria and itching are usually absent.

- ACE inhibitors can also cause intestinal edema, and the sudden onset of abdominal pain, diarrhea, and vomiting in an older adult should prompt inquiries about the use of ACE inhibitors [18-22]. Most reported cases have occurred in older women and involved the small bowel, with abdominal CT demonstrating dilated and thickened loops of small bowel with ascites or subobstruction [19,21]. Recognition of this complication of ACE inhibitor therapy can spare the patient unnecessary surgical intervention.

Many cases of ACE inhibitor-induced angioedema occur within one week of beginning therapy or increasing the dose [9,16], but others may occur up to several years later [9,13,17]. (See "Major side effects of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers".)

Discontinuation of ACE inhibitors usually results in no further episodes of angioedema or a marked decrease in the frequency and severity of subsequent episodes. In one series of 54 patients with angioedema while taking an ACE inhibitor, 85 percent had no further events or improved dramatically after switching to another antihypertensive drug (21 patients changed to an ARB) [23]. In the remaining eight patients who did not improve, another cause was identified for angioedema in six patients, and two had recurrent episodes of angioedema which ceased after discontinuation of the ARB. All patients in this study were evaluated for underlying complement disorders, and no abnormalities were found.

A small number of reports have noted that the risk of angioedema remains increased for several months after a patient has stopped taking ACE inhibitors, suggesting that the biochemical changes take time to normalize after the drug is discontinued [12,23,24]. This phenomenon may complicate studies of recurrence soon after stopping ACE inhibitors.

There is a significant risk of recurrent angioedema if ACE inhibitors are continued, as shown in a report of 82 patients who had a first episode of angioedema while on an ACE inhibitor [25]. The risk of recurrence was much higher in those with continued exposure to ACE inhibitors compared to those who were switched to other agents (19 versus 2 per 100 patient years). Review of the medical records of those who were continued on ACE inhibitors revealed that clinicians often attributed the angioedema to other causes, even after multiple recurrences.

- Mechanism — Angioedema induced by ACE inhibitors is a class effect that is directly related to the mechanism of action. ACE inhibitor-induced angioedema is primarily mediated by kinins. Angiotensin converting enzyme (ACE, also called kininase II) has at least two physiologic functions. It catalyzes the conversion of angiotensin I to angiotensin II (a vasoconstrictor that increases blood pressure), and it degrades bradykinin (a potent vasodilator) (figure 1).

Thus, ACE inhibitors have the effects of decreasing angiotensin II and increasing bradykinin [8,9]. In the presence of ACE inhibition, bradykinin can accumulate and interact with vascular bradykinin B2 receptors, causing vasodilation, increased vascular permeability, increased c-GMP, and release of nitric oxide. One report described a patient with ACE inhibitor-induced angioedema whose bradykinin levels rose acutely during the episode and normalized after [26].

There are other metabolic pathways that degrade bradykinin more slowly. Genetic deficiencies in these pathways could predispose selected patients to the development of angioedema when bradykinin levels are enhanced following administration of an ACE inhibitor. One such pathway involves the enzyme aminopeptidase P. Patients with a history of angioedema upon exposure to an ACE

inhibitor may have lower plasma concentrations of aminopeptidase P compared with similarly treated patients who did not develop angioedema [27,28].

At the time of this review, there are no tests that can identify patients at higher risk for ACE inhibitor-induced angioedema in advance of administration [29]. However, these drugs should be avoided in patients with previous episodes of unexplained angioedema or with known hereditary or acquired angioedema.

Angiotensin II receptor blockers — A number of reports have linked the use of angiotensin II receptor blockers (ARBs), such as losartan, valsartan, and telmisartan, with the development of angioedema, although the risk appears to be lower than with ACE inhibitors [6,30,31]. In the largest comparative study, the ONTARGET trial of over 17,000 patients treated with telmisartan or ramipril, the rate of angioedema was significantly lower with telmisartan (0.1 versus 0.3 percent) [6]. The develop of angioedema following therapy with ARBs is surprising since these drugs are not thought to affect kinin metabolism directly (figure 1).

ARBs appear to be a safe alternative for the majority of patients who develop ACE inhibitor-associated angioedema [17,32]. This issue was addressed in a trial of 5926 patients who were intolerant to ACE inhibitors for various reasons, including 75 patients with angioedema or anaphylaxis [32]. All patients were randomly assigned to receive either an ARB (telmisartan) or placebo. After a median follow-up period of 54 months, none of the patients receiving telmisartan developed angioedema.

Despite these observations, some patients who have had angioedema associated with ACE inhibitors develop recurrent angioedema while being treated with an ARB [17,23,31,33]. Thus, patients who are switched from an ACE inhibitors to an ARB following angioedema should be counseled that there is a small chance of recurrence and given clear instructions on how to proceed should this occur.

ACE inhibitors and ARBs may also unmask hereditary or acquired deficiency of C1 inhibitor, as discussed in the next section [8,33-35].

Hereditary and acquired angioedema — Angioedema can occur in patients with abnormalities in the level or function of the regulatory complement protein C1 inhibitor (C1-INH, previously referred to as C1 esterase inhibitor) in association with increased levels of bradykinin. These disorders are reviewed in detail separately. (See "Clinical manifestations and pathogenesis of hereditary angioedema" and "Acquired C1 inhibitor deficiency: Clinical manifestations, epidemiology, and pathogenesis".)

Summarized briefly, both hereditary and acquired forms of C1-INH deficiency exist, with similar clinical manifestations. The main differences between the two conditions are the age of presentation and the underlying health of the patient:

- Patients with hereditary angioedema typically present in late childhood or early adolescence with angioedema following trauma, infection, dental procedures, or emotional stress, with an increasing frequency and severity of episodes with puberty, menses, and ovulation. These patients are otherwise healthy.

- In contrast, the acquired form typically occurs at an older age and most patients have an associated lymphoproliferative disorder.

The symptoms with either form of C1-INH deficiency range in severity from a minor inconvenience to life-threatening laryngeal edema.

Estrogens — There is a form of familial angioedema that presents similarly to hereditary angioedema, but affects women more often than men, particularly following exposure to estrogens. This disorder appears to be caused in some families by a mutation causing a gain in function in coagulation factor XII. Polymorphisms in the genes encoding enzymes that degrade bradykinin have also been reported. Complement studies are normal, including C4 and C1 inhibitor level and function. Exposure to estrogens, either through contraception, hormone replacement therapy, or pregnancy, may trigger attacks of angioedema in affected patients. This disorder is reviewed separately. (See "Clinical manifestations and pathogenesis of hereditary angioedema", section on 'Hereditary angioedema with normal C1 inhibitor'.)

Etiologies of unknown mechanism — There are several recognized causes of angioedema for which mechanisms are not defined. The treatment of these disorders is reviewed separately. (See "An overview of angioedema: Clinical features, diagnosis, and management".)

Idiopathic angioedema — Idiopathic angioedema is the term applied to recurrent episodes of angioedema without urticaria, for which no explanation can be found after a thorough evaluation to exclude allergic disorders, drug reactions, and defects in complement pathways. The management of idiopathic angioedema is presented elsewhere. (See "An overview of angioedema: Clinical features, diagnosis, and management".)

Calcium channel blockers — Angioedema, either of the skin or small bowel, has been reported in association with the use of calcium channel blockers, both dihydropyridines (eg, amlodipine, nifedipine) and non-dihydropyridines (eg, diltiazem and verapamil) [36-40]. The mechanism is unknown.

Fibrinolytic agents — Angioedema without urticaria has been reported following fibrinolysis with streptokinase and alteplase in patients treated acutely for stroke and thrombosis [41,42]. This complication is discussed separately. (See "Fibrinolytic (thrombolytic) therapy for acute ischemic stroke", section on

'Angioedema'.)

Other drugs — Other drugs that have been reported to cause angioedema without urticaria include sirolimus and everolimus, amiodarone, metoprolol, risperidone, paroxetine and etanercept, and other biological agents [43-51].

Other rare causes — Other rare causes of angioedema include selected disorders with eosinophilia and urticarial vasculitis.

- Disorders with eosinophilia — Angioedema is associated with a peripheral eosinophilia in two disorders, the hypereosinophilic syndrome and Gleich syndrome.

- Approximately 15 percent of patients with the hypereosinophilic syndrome have angioedema and this diagnosis should be considered in patients with dramatic elevations in peripheral eosinophil counts (eg, ≥1500 eosinophils/microliter) [52,53]. The mechanisms of the angioedema in this disorder may involve the direct release of vasodilatory mediators from eosinophils or may reflect the activation of cutaneous mast cells by eosinophil-derived mediators.

(See "Clinical manifestations, pathophysiology, and diagnosis of the hypereosinophilic syndromes".)

- Gleich syndrome presents with episodic angioedema, urticaria, fever, pruritus, weight gain, elevated serum IgM, and leukocytosis with marked blood eosinophilia. This is discussed elsewhere.

(See "Diseases with eosinophilic involvement of specific organs", section on 'Episodic angioedema with eosinophilia'.)

- Urticarial vasculitis — Angioedema may be observed in patients with hypocomplementemic urticarial vasculitis [54,55]. The urticarial lesions of urticarial vasculitis are variably painful, ecchymotic, and purpuric, and often leave residual bruising upon resolution. Systemic disease and fever may be present. (See "Urticarial vasculitis".)

SUMMARY

- Angioedema is self-limited, localized swelling of the skin or mucosal tissues. Angioedema may occur in isolation, accompanied by urticaria, or as a component of anaphylaxis.

- Angioedema results from a loss of vascular integrity, allowing fluid to move into the interstitial tissues, due to the presence of inflammatory mediators. (See 'Pathogenesis' above.)

- The causes of angioedema can be divided into three groups based upon the underlying mechanism (see 'Causes' above:

  - Mast cell mediated-angioedema, such as allergic reactions, NSAIDs, agents that directly activate mast cells (see 'Mast cell-mediated etiologies' above).

  - Bradykinin-mediated angioedema, such as ACE inhibitors and hereditary and acquired forms of C1 inhibitor deficiency. (See 'Bradykinin-mediated etiologies' above.)

  - Causes with unknown mechanisms, such as calcium channel blockers, fibrinolytic agents, neonatal parvovirus infection, and urticarial vasculitis. (See 'Etiologies of unknown mechanism' above.)

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GRAPHICS

Major causes of mast cell-mediated angioedema

IgE-dependent allergic reactions
Foods
Drugs (antibiotics, local anesthetics, hormones)
Stinging insects
Latex
Contact (fresh fruits and vegetables, animal saliva)
Direct mast cell mediator release
Opiates
Muscle relaxants (succinylcholine, curare)
Radiocontrast agents
Perturbations in arachidonic acid metabolism within mast cells
Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs)

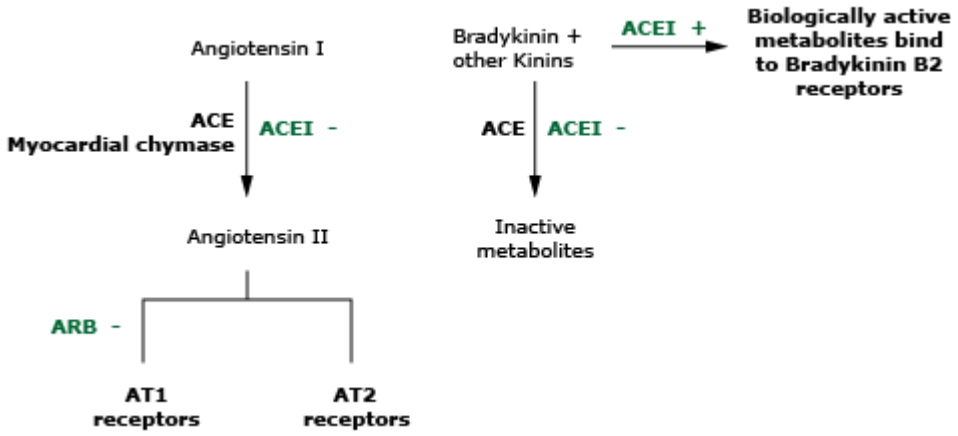
Gell and Coombs classification of immunologic reactions

Type	Description	Mechanism	Clinical features
I Immediate reaction (within 1 hour)	IgE-mediated, immediate-type hypersensitivity	Antigen exposure causes IgE-mediated activation of mast cells and basophils, with release of vasoactive substances such as histamine, prostaglandins, and leukotrienes.	Anaphylaxis Angioedema Bronchospasm Urticaria (hives)
II	Antibody-dependent cytotoxicity	An antigen or hapten that is intimately associated with a cell binds to antibody, leading to cell or tissue injury	Hemolytic anemia Thrombocytopenia Neutropenia
III	Immune complex disease	Damage is caused by formation or deposition of antigen-antibody complexes in vessels or tissue. Deposition of immune complexes causes complement activation and/or recruitment of neutrophils by interaction of immune complexes with Fc IgG receptors	Serum sickness
IV	Cell-mediated or delayed hypersensitivity	Antigen exposure activates T cells, which then mediate tissue injury. Depending upon the type of T cell activation and the other effector cells recruited, different subtypes can be differentiated (ie,	Contact dermatitis, some morbilliform reactions, severe exfoliative dermatoses (eg, SJS/TEN), AGEP, DRESS/DiHS, interstitial nephritis, drug-induced hepatitis, other presentations

		Types IVa-IVd)	

SJS/TEN: Stevens-Johnson syndrome/ Toxic epidermal necrolysis
AGEP: Acute generalized exanthematous pustulosis
DRESS/DiHS: Drug rash with eosinophilia and systemic symptoms/Drug-induced hypersensitivity syndrome *Adapted from: Weiss, ME, Adkinson, NF. Immediate hypersensitivity reactions to penicillin and related antibiotics. Clin Allergy 1988; 18:515.*

Actions of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers on angiotensin and kinin pathways



ACE: angiotensin converting enzyme; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker.